Program Announcements (PA'S)

MOLECULAR BIOLOGY OF SKELETAL MUSCLE AND ITS DISEASES
NIH GUIDE - Vol. 20, No. 22, June 7, 1991

PA: PA-91-65

P.T. 34; K.W. 0705050, 1002004, 0760070, 1002058, 1003018, 0775000, 745030

National Institute of Arthritis and Musculoskeletal and Skin Diseases

INTRODUCTION

The Muscle Biology Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on skeletal muscle, its diseases and disorders. This includes studies on normal muscle structure, function, development, and homeostasis. NIAMS, through this program announcement, encourages submission of grant applications in the specific area of molecular events responsible for muscle specialization during development, regeneration, and reconstruction, including changes induced by patterns of muscle activity.

BACKGROUND

Skeletal muscle is a major tissue of the human body, responsible for 40 percent of total body weight in normal adults. Its primary function is generating and controlling body motion and maintaining body posture. Extensive observation and research, motivated by this major role, have enhanced our understanding of many aspects of muscle action. Skeletal muscle has many unique properties as a tissue, with enzymatic, mechanical, and thermal properties that are easy to control and measure. These properties can be changed; muscle responds rapidly to patterns of use or disuse by modifying the total contractile protein content and by shifting relative concentrations of various alternative forms.

Skeletal muscle precursor cells are established early in development via processes involving one or more myogenic determination factors (the myd1 gene product, MyoD, myogenin, myf5, and mrf4). The mechanisms by which these factors are initially induced and by which they cause pluripotential mesodermal cells to enter the myogenic cell lineage are not understood. Early myoblasts are apparently interchangeable, in that factors responsible for specialization are acquired during development from external cues such as location and activity.

Studies of muscle gene regulation have concentrated upon identifying muscle-specific control elements and the myogenic transcription factors with which they interact. DNA sequence motifs that are common to many muscle genes are

known to affect muscle gene expression, but knowledge of gene-specific and modulatory control elements is lacking. Transcription mediated via the common control elements appears to involve interactions with protein complexes composed of both myogenic and ubiquitous nuclear factors. In myoblasts, the activity of these complexes is controlled by environmental factors such as mitogens, but neither the mechanism of this process nor how the expression of specific muscle genes is modulated in differentiated muscle cells is understood.

There has been considerable success recently in sequencing the coding regions for muscle proteins, including the characterization of many genes that can be transcribed in various ways (alternative splicing) to produce considerable isoform diversity for each protein. In many cases, such as the contractile proteins, several isoforms are present within single muscle fibrils. Considerable efforts are being made to identify and characterize factors that promote or inhibit expression of various isoforms and the ways these factors interact with genetic material. Changes in rates of expression and alterations in splicing have major impact on the reconstruction of muscle that occurs in response to patterns of activity.

Other major contractile, regulatory, and structural proteins have been isolated and characterized. Molecular genetic techniques allow for altering sequences and hence provide a way to explore the functional contributions of different parts of proteins. Such techniques are already being used to explore the protein chemistry of calcium binding and transport in troponin-C and the membrane calcium ATPase transport protein.

RESEARCH GOALS AND SCOPE

The purpose of this program announcement is to encourage the submission of high-quality applications that further increase our knowledge of the molecular biology of skeletal muscle and its diseases. This includes, but is not restricted to, the following specific areas:

- Studies characterizing genes of muscle proteins, substances, and membranes. Examples are the proteins of force production and regulation, including actin, myosin, tropomyosin, troponin; calcium binding proteins, such as calmodulin; ion channel proteins; cytoskeletal proteins, such as spectrin, actinin, dystrophin; surface receptors, and substances of the basal lamina and extracellular matrix.

- Mechanistic molecular genetic studies of muscle protein functions.

- Studies on nuclear factors that promote or inhibit gene expression and transcription in muscle during development, regeneration, and response to altered levels of muscle activity

(e.g., isoform switching).

- Studies to determine mechanisms whereby external factors, such as growth hormones or signal transduction, influence transcriptional regulation and the expression of alternate isoforms.

- Studies on the genetic basis of inherited diseases of skeletal muscle, its membranes, and its constituent proteins.

- Studies of possible therapies and clinical interventions that are based on modifying genetic expression in muscle. Such studies should be focused on understanding mechanisms by which such interventions alter cellular function.

Investigators are encouraged to use the full range of current disciplines and techniques, including biochemistry, biophysics, molecular genetics, recombinant techniques, and cell biology.

MECHANISM OF SUPPORT

Applicants may apply for research project grants (R01), program project awards (P01), First Independent Research Support and Transition (FIRST) (R29) awards, and fellowships and research career development awards.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed and assigned in accordance with the usual Public Health Service peer review procedures. Review criteria include significance and originality of the research goals and approaches; feasibility of the research and adequacy of the experimental design; training, research competence, and dedication of the investigator(s); adequacy of available facilities; and provision for the humane care of animals. Funding decisions will be based on initial review group and National Advisory Council recommendations.

Applications must be submitted on form PHS 398 (rev. 10/88) or the training/fellowship application form, available in the business or grants office at most academic or research institutions, and from the Division of Research Grants, National Institutes of Health, telephone (301) 496-7441. Applications will be accepted in accordance with the submission dates for research applications on a continuing basis: February 1, June 1, October 1. Fellowship receipt dates are January 10, May 10, September 10.

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH

POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH and ADAMHA policy is that applicants for NIH/ADAMHA clinical research grants and cooperative agreements will be required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale should be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information should be included in the form PHS 398 in Section 2, A-D of the Research Plan AND summarized in Section 2, E, Human Subjects. Applicants/offerors are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, Hispanics).

The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research includes human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the

relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

The phrase "MOLECULAR BIOLOGY OF SKELETAL MUSCLE AND ITS DISEASES, PA-91-65" must be typed on line 2 of the face page of the application form PHS 398. The original and six copies must be sent or delivered to:

Grant Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, MD 20892-4500**

The original and two copies of the fellowship application must be sent to the DRG address above.

For further information, investigators are encouraged to contact the following individual:

Richard W. Lymn, Ph.D.
Muscle Biology Program Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 403
Bethesda, MD 20892
Telephone: (301) 402-3346 (Change to 301-594-9959, effective March 29, 1993)

For fiscal and administrative matters, contact:

Diane Watson
Grants Management Officer

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 417E
Bethesda, MD 20892
Telephone: (301) 402-3352

This program is described in the Catalog of Federal Domestic Assistance No.93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, administered under PHS grants policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

**THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH.
APPLICANTS WHO USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD BUILDING IS:

5333 Westbard Avenue
Bethesda, Maryland 20816